

EDITORIAL COMMENT

Plaque Temperature, Arterial Remodeling, and Inflammation

Understanding “Hot-Spots” in the Coronary Arteries*

Paul Schoenhagen, MD, FAHA

Cleveland, Ohio

Atherosclerosis and its cardiovascular complications remain the leading cause of death in modern societies. Our pathophysiologic understanding of disease progression has significantly evolved and focused interest on the early detection of vulnerable lesions, which are ultimately responsible for a majority of acute coronary and cerebrovascular events (1). There is evolving evidence from basic and clinical research that some of these ubiquitous coronary hot-spots are suddenly activated and rupture, causing acute events, whereas others are associated with asymptomatic disease progression. However, much like volcanic hot-spots, time, severity, and location of “eruption” can not be predicted with certainty.

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Two particular interesting aspects in the progression of these vulnerable lesions are the role of inflammation and arterial remodeling (2,3). Based on a detailed understanding at the cellular and molecular level, the inflammation hypothesis of atherosclerosis has evolved from bench to bedside, and inflammatory serum markers such as C-reactive protein (CRP) are part of cardiovascular risk assessment (4). Arterial remodeling was first described as an adaptive process of coronary artery expansion maintaining luminal size during early plaque accumulation (5). Subsequent histologic and in vivo studies with intravascular ultrasound (IVUS) examined the relationship between clinical presentation and direction of remodeling. Surprisingly, the expansion of the vessel at the lesion site (expansive or positive remodeling) was found to be associated with inflammation, plaque vulnerability, and acute clinical presentation (3,6,7).

In this context, Casscells et al. (8) demonstrated in the mid-1990s that local coronary temperature measurements would allow locating foci of inflammation. This has since been validated in single-center clinical studies, with eminent contributions by the group of Stefanadis et al. (9), who conducted early human intracoronary thermographic studies in the late 1990s. Using a relatively large single-channel catheter, the temperature differences between atherosclerotic plaque and adjacent normal vascular wall was $0.10 \pm 0.11^\circ\text{C}$ in patients with stable angina, $0.68 \pm 0.34^\circ\text{C}$ in those with unstable angina, and $1.47 \pm 0.69^\circ\text{C}$ in patients with acute myocardial infarction. In subsequent studies the same investigators found a significant correlation between CRP and temperature heterogeneity (10).

In the current issue of the *Journal*, Toutouzas et al. (11) describe an intriguing comparison of simultaneous IVUS and thermography findings in coronary lesions of patients presenting with stable and unstable coronary syndromes. The authors find a correlation between morphologic features of vulnerability, including rupture and remodeling, with an increase in lesion temperature difference. Interestingly, although plaque rupture was associated with increased temperature difference in both stable and unstable patients, positive remodeling was associated with increased temperature only in unstable patients.

These results provide important insights into the potential use of in vivo catheter-based technology for the identification of focal treatment targets and serial assessment during systemic pharmacologic intervention. Previous serial studies have already shown focal changes of remodeling and temperature difference during statin therapy (12,13). However, a critical question facing catheter-based diagnostic modalities remains if measurements should be performed locally or along the entire artery segment. For example, local lumen wall temperature is influenced by a complex interaction between heat-producing macrophages in the shoulder region, the insulating properties of the lipid core, and the heat-dissipating properties of vasa vasorum, resulting in a highly focal distribution of temperature differences (14). For a detailed focal analysis, an optimal catheter would require a high spatial resolution of temperature measurements. On the other hand, there is overwhelming evidence of the systemic nature of vulnerability (2). Using catheter-based technology, this has been confirmed showing global inflammatory activation (15), multifocal plaque rupture (16,17), and elevated plaque temperature of lesions remote from the culprit site (18). For the assessment of a systemic process, a catheter pullback through the entire segment is required, allowing the observation of volumetric end points (19).

This has important implications for catheter design and end point specification. The large catheter used by Stefanadis et al. (9) measures temperature at a focal lesion site mostly during obstruction of blood flow. However, obstruction of blood flow and its “cooling effect” on coronary wall temperature significantly increases the degree of detected

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Division of Radiology and Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio.

temperature heterogeneity (20). Other recent studies with nonoccluding thermography catheters, allowing real-time cross-sectional thermal mapping of the arterial wall without flow interruption, were in fact unable to detect temperature increases in patients with acute coronary syndromes (21).

Although the current results provide important insights into plaque vulnerability, further validation and standardization of methodologic details are necessary. Similar to the development of the IVUS end point of volumetric plaque burden, it is necessary to evaluate volumetric remodeling (22) and global thermal burden (global plaque warming). These and other details have already been proposed for the design of prospective serial thermography multicenter trials (23). Until such studies are performed, application in clinical practice has to proceed with caution, keeping in mind that, much like their geologic counterparts, coronary hot-spots are difficult to pinpoint and even more difficult to control.

Reprint requests and correspondence: Dr. Paul Schoenhagen, Division of Radiology, Department of Cardiovascular Medicine, The Cleveland Clinic, Cardiovascular Imaging, Desk HB-6, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: schoenp1@ccf.org.

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